Poster 24: Modeling Personalized Radiotherapy in Endometrial Cancer: Genomic Associated Radiation Dose (GARD) Across Molecular Subtypes

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Topic
Endometrial

Objectives
There has been a paradigm shift in the use of targeted therapeutics derived from molecular classification, however radiotherapy (RT) remains largely empiric. The Genomic Associated Radiation Dose (GARD) – derived from Radiation Sensitivity Index (RSI) which is a linear regression model derived from a 10-gene expression signature prognostic of intrinsic tumor radiosensitivity. Although developed on NCI-60 cancer cell line panel, endometrial cancer (EC) cell lines were not included. RSI/GARD values concordance across microarray and modern RNA sequencing (RNAseq) platforms remain unknown. We sought to compare platform derived GARD values in EC cell lines and correlate these with PRoMisE defined molecular subtypes.

Methods
Raw RNAseq data from EC cell lines were obtained from the NCBI sequence read archive (PJRNA523380) and processed to calculate RSI. Microarray analysis using the Clariom S platform was performed on RNA extracted from EC cell lines. RSI values from both platforms were used to calculate GARD across three clinically relevant RT dose regimens: external beam radiation therapy (EBRT) (EQD2 44.25 Gy), vaginal brachytherapy (VBT) (EQD2 29.75), and combined EBRT with vaginal boost (EQD2 63 Gy). GARD distributions were visualized using violin plots stratified by expression platform, with individual data points annotated by PRoMisE molecular subtype.

Results
We analyzed 10 EC cell lines using microarray and 21 EC cell lines using RNAseq. Across both platforms, standard RT dosing revealed significant heterogeneity in GARD values. For EBRT alone (EQD2 44.25 Gy), median GARD was 14.3 (range 1.9–44.4) by RNAseq and 28.9 (range 18.0–31.2) by microarray. For combined EBRT with vaginal boost (EQD2 63 Gy), median GARD was 20.3 (range 2.6–63.3) by RNAseq and 41.2 (range 25.7–44.4) by microarray. PRoMisE subtypes included 1 NSMP and 9 dMMR (5 with concurrent p53 abnormality) in the microarray cohort, and 1 POLE, 15 dMMR, and 5 p53 abnormal in the RNAseq cohort; 10 dMMR and the POLE line were dually classified as p53 abnormal.

Conclusions
GARD in endometrial cancers is heterogenic, challenging uniform radiation dosing and supporting dose personalization. Further study should be done for clinical validation integrating molecular subtype and GARD based RT selection.

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